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Interferon Treatment of Chronic Active Hepatitis C During Therapy of Acute Lymphoblastic Leukemia

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Due to concerns that antineoplastic therapy produces prolonged decrease in immune function, interferon treatment of chronic active hepatitis C (CAHC) has been used only at one year or longer after the end of cancer therapy. We report the experience of an 11-year-old who developed symptomatic CAHC at the start of maintenance therapy for testicular relapse of acute lymphoblastic leukemia (ALL). Significant dose reduction of maintenance therapy did not improve the tolerance of antileukemic treatment. In an effort to improve his liver disease and to deliver effective antileukemic therapy, interferon alpha and an alternative maintenance therapy regimen for ALL were initiated. The patient tolerated the combined therapy well. Interferon therapy was continued for 27 months, which was three months from the end of antineoplastic therapy. At that time serum transaminase values were normal, and no HCV viral genome was detectable. Viral genome was detected 10 months later. The combined effects of interferon and antineoplastic therapy resulted in myelosuppression requiring dose reduction of both treatments. The patient remains asymptomatic and with no evidence of recurrent leukemia more than six years from diagnosis of relapse. The effect on the status of this patient's CAHC was similar to that reported among leukemic patients who underwent an interferon course more than one year from the end of antineoplastic therapy. Interferon treatment of CAHC can be given concomitantly with antineoplastic therapy. Am. J. Hematol. 61:130–134, 1999.

Key words: hepatitis C; interferon; acute lymphoblastic leukemia

INTRODUCTION

Hepatitis C virus (HCV) is the etiologic agent of as much as 90% of posttransfusion hepatitis prior to 1990 [1,2]. Individuals with acute lymphoblastic leukemia (ALL) are at risk for HCV infection since they usually receive at least one, and typically multiple, transfusions of blood products during the course of their disease [3]. The frequency of antibody to HCV in children with leukemia ranges from 1 to 43% [4–7]. Reports of interferon treatment of chronic active viral hepatitis have stressed the importance of waiting as long as two years after the completion of antineoplastic therapy to ensure immune competence [8,9]. There are no prior reports of the use of interferon-α concomitant with cytotoxic antileukemic therapy.

We report on a patient who had jaundice, malaise, antibody to HCV, and the histologic appearance of chronic active hepatitis at the time of testicular relapse of ALL. During systemic therapy for testicular relapse, he developed transaminase elevation to greater than 15 times normal and total bilirubin (TB) greater than 6.0 mg/dl. Recombinant interferon-α2a (Ifn-α) was initiated to treat his liver disease and to allow effective antileukemic therapy to be delivered. The patient tolerated Ifn-α therapy well, and completed systemic treatment for testicular relapse of ALL.

CASE REPORT

In October 1988 the patient was eight years old when he was diagnosed with B-cell precursor ALL. He was treated according to a contemporary protocol (Pediatric Oncology Group #8602 regimen C). During the first 20 weeks of therapy he received eight units of packed red

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blood cells and 58 units of random donor platelets. Symptoms of hepatitis were not manifest until week 137 of treatment when he developed prolonged malaise, lethargy, vomiting, and diarrhea. At that time his alanine amino transferase (ALT) / aspartate aminotransferase (AST) were 130/124 and his TB was 4.8 mg/dl. Antibody to hepatitis A virus, hepatitis B surface antigen, and core protein were not detected, nor was hepatitis B surface antigen. HCV serology using a first generation ELISA assay was positive. The treating physician chose to stop maintenance at week 142 of a planned 156 week course due to the serologic diagnosis of HCV, the symptoms of hepatitis, and poor tolerance of maintenance leukemic therapy. Off therapy evaluation showed no evidence of leukemia in bone marrow or cerebrospinal fluid (CSF) and a normal physical exam.

One month after stopping therapy, a routine physical exam showed that both testes were increased in size and hard. Testicular biopsy showed a leukemic infiltrate. During the same anesthesia a liver biopsy was done. This showed hepatocellular necrosis with grade 2 periportal inflammation, and stage 2 portal fibrosis with focal areas of stage 3 bridging fibrosis [10]. Repeat bone marrow and CSF exam were normal. The patient underwent 2500 cGy radiation therapy to the testes and standard four-drug systemic reinduction for ALL. Consolidation consisted of cyclophosphamide 1 gm/M^2/dose on days 1 and 14, daily oral 6-mercaptopurine (6-MP) 50 mg/M^2, and four-day courses starting days 1, 8, 15, and 22 of cytosine arabinoside (Ara-C) 75 mg/M^2/d IV. A week prior to liver biopsy ALT/AST were 293/192. One week after liver biopsy, at the start of induction therapy, ALT/AST/TB were 925/736/1.0. At the end of induction or start of consolidation ALT/AST/TB were 447/175/0.8.

Planned maintenance therapy was daily oral 6-MP (50 mg/M^2); weekly oral methotrexate (MTX) 20 mg/M^2, and every four weeks vincristine and five-day prednisone 40 mg/M^2/d. Central nervous system prophylaxis was with intrathecal MTX and oral MTX was not given during that week. At the beginning of maintenance ALT/AST/TB were 125/89/0.6. MTX was given IT during week one of maintenance therapy, and the first oral MTX was given at week two. At the start of week three ALT/AST/TB were 101/90/3.6, and the patient complained of mild to moderate malaise. 6-MP and MTX were held due to elevated TB. One week later AST/ALT/TB were 289/178/1.7, and oral medication was resumed at 25% and 17% of the planned 6-MP and MTX dose, respectively. After one week of this dose schedule AST/ALT/TB were 984/490/1.2.

Due to the need for systemic ALL therapy and the poor tolerance of even small fractions of the intended doses of 6-MP and MTX, an alternative therapeutic approach was pursued. Ifn-α therapy was initiated at a dose of 1 million units (MU) subcutaneously (0.66 MU/M^2) three days per

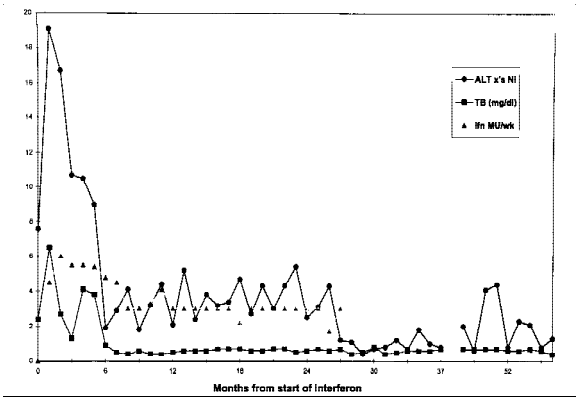

Fig. 1. Patient's serum alanine amino transferase (ALT) represented as actual value/upper limit of institutional normal range or times normal (x's Nl); serum total bilirubin (TB) represented as actual values, and interferon (Ifn) dose per week in million units (MU).

week. This dose was increased with one intermediary step to 2.0 MU per dose (1.32 MU/M^2/dose) three days per week (see Figure 1). Maintenance antileukemic therapy was altered to decrease the exposure to hepatotoxic agents. It utilized noncross resistant pairs of drugs and consisted of etoposide 150 mg/M^2/dose IV, Ara-C 300 mg/M^2/dose IV alternating every four weeks with cyclophosphamide 600 mg/M^2/dose, vincristine 1.5 mg/M^2/dose and five-day prednisone 40 mg/M^2/day [11]. Secondary to prolonged neutropenia and thrombocytopenia the standard doses of 150 mg/M^2 of etoposide and 300 mg/ M^2 of Ara-C were reduced to 100 mg/M^2/dose and 150 mg/M^2/dose, respectively. Vincristine was not given when total TB was greater than 1.5 mg/dl. Ifn-α dose was adjusted to maintain platelets greater than 75,000/mm^3 and neutrophils greater than 1,000/mm^3. Ultimately, this resulted in a dose of Ifn-α of 1.5 MU two days per week. From month 7 to month 27 the Ifn-α dose per M^2 per week varied from 1.9 to 1.74 MU due to delivery of a constant dose with growth in body surface area. Maintenance leukemia therapy was continued for a total of 24 months. The patient continued to receive Ifn-α therapy until one month after his ALT had decreased to within the normal range, at which time reverse transcriptase-polymerase chain reaction (RT-PCR) for HCV was negative. This was three months after the end of cytotoxic leukemia therapy resulting in a total of 27 months of Ifn-α therapy. Repeat RT-PCR for HCV was positive at months 37 and 53. Androgen replacement therapy was begun after completion of the antileukemic therapy. The patient remains in remission 72 months from testicular relapse. Current clinical status including activity level and growth is normal. His peripheral blood counts are normal with the exception of a platelet count between 90,000 and 140,000/mm^3. A bone marrow exam one year from the end of leukemia therapy and nine months from

the end of interferon therapy showed normal cellularity with slightly decreased megakaryocyte number.

DISCUSSION

We have described the clinical course of a patient with ALL who was diagnosed with chronic active hepatitis C (CAHC) simultaneous with diagnosis of an early, isolated, testicular relapse of ALL. Although ALL induction and consolidation therapy were well tolerated he showed clinical and laboratory signs of exacerbation of CAHC during the maintenance phase of therapy. Ifn-α and alternative ALL maintenance therapy were used simultaneously. Low platelet and neutrophil number required dose alteration for both Ifn-α and cytotoxic chemotherapy, but the treatments were otherwise well tolerated. This is the first reported experience with simultaneous administration of cytotoxic therapy for ALL and Ifn-α for CAHC.

HCV infection is rare in the pediatric age group. Two large studies found similar frequencies of 0.05 and 0.1% of antibody to HCV among general adolescent populations in the United States [12,13]. Individuals who receive blood products, including those with malignancies [14,15], hemophilia [16,17], sickle cell disease [18], and thalassemia [19,20] have a higher incidence of antibody to HCV compared with the general population. The impact of HCV infection on the tolerance of simultaneous therapy and the natural history of these diseases is only beginning to be defined. A retrospective study of 87 southern Italian children at the end of their treatment for ALL found that 32% were HCV antibody positive. Those with antibody to HCV had more frequent elevation of ALT and TB and had more frequent interruption of maintenance ALL therapy (82% versus <2%) compared with the ALL patients who were HCV antibody negative. Five of the 28 patients with HCV antibody developed signs of chronic liver disease [7]. The frequency of HCV infection among these children from southern Italy is similar to the 43% reported among 102 children with ALL from northern Italy [6]. However, it is in marked contrast to the finding of 1 of 98 children with hematologic malignancies from central England who had anti-HCV antibody or had detectable HCV by RT-PCR [4] and the 13% of 24 children with acute leukemia who were antibody positive against HCV from Massachusetts [14].

Ifn-α was established as a therapy that was effective for some adult patients with chronic active non-A, non-B hepatitis prior to the identification of the HCV [21,22]. Since then the experience with more than 1,800 adult patients has been reported, allowing clearer recommendations for dose schedule and selection of patients [23–25]. The use of Ifn-α in children with CAHC was first reported by Ruiz-Moreno et al., who treated subjects who had no underlying disease with 3 MU/M^2 Ifn-α three times per week for six months. Five of the 11 evaluable patients had normal values for ALT and eight were negative for HCV RNA at 24 months from the start of treatment. All children were reported to have an improvement in their liver histology [26]. The optimal dose, timing, and strategy for use of Ifn-α in children with HCV infection is not yet defined. Eight additional studies of Ifn-α for children with CAHC have been reported [8,27–33]. The frequency of sustained complete response defined as absence of detectable viral genome and normal ALT typically at 12 months after the end of treatment has consistently been in the range of 30 to 40%. The most relevant experience to our patient is that of Komatsu et al., who treated 13 individuals, who had completed leukemia therapy, with Ifn-α for CAHC. All subjects were at least two years from the end of leukemia therapy due to a concern that the cytotoxic chemotherapy may cause a prolonged immunosuppressed state and that immunocompetence was necessary for Ifn-α efficacy. These children were given 1 MU per kg to a maximum of 6 MU daily for two weeks and then three times per week for an additional 22 weeks. Prior to Ifn-α therapy all children had detectable HCV genome by RT-PCR and had ALT above normal. Twelve months after completion of Ifn-α therapy four of 13 were negative for the viral genome and eight of 13, including all RT-PCR negative patients, had normal ALT values. Complications of Ifn-α therapy included an influenza-like syndrome in all children that generally lasted less than 10 days; slight, transient hair loss in two children and a "small" decrease in leukocyte and platelet count in all children, that did not necessitate dosage reduction [8].

Acute adverse effects of treatment for our patient were mild malaise and myalgia for four weeks duration, grade two thrombocytopenia and grade three and four neutropenia. However, the assessment of the myelosuppressive effect of Ifn-α is confounded by the simultaneous administration of cytotoxic therapy. He also has chronic grade 1 thrombocytopenia. The mechanism of myelosuppression may be a direct effect of Ifn-α on bone marrow progenitor cells [34]. In one series of patients with CAHC treated with Ifn-α the reported frequency of grade 3 thrombocytopenia was 10% and grade 3 neutropenia was 20% [35]. Ultimately the tolerated dose of Ifn-α for our patient in the context of leukemic therapy was 1.5 MU two days per week (mean dose of 1.8 MU/M^2 per week), which was 20% of a recommended dose of 9 MU/M^2 per week. At this interferon dose it was possible to deliver 67% of planned leukemic maintenance therapy. Thus, the simultaneous treatment of hepatitis and leukemia did compromise the drug delivery for the individual diseases. Additionally, Ifn-α may have had some antileukemic effect in view of clinical and in vitro data indicating efficacy of Ifn-α against ALL [36–38]. The strategy employed to provide an adequate treatment

of hepatitis was to continue the drug to a biological endpoint of normalization of ALT value. This resulted in a prolonged (27 months), but low-dose course. The total dose delivered was 240 MU/M^2, which is similar to the total dose used by Ruiz-Monero et al. [26] and Komatsu et al. [8] but distributed over a longer time.

Dose intensity, defined as the amount of drug delivered per period of time, may be significant when considering patients who develop CAHC during treatment for ALL. Dibenedetto et al. described an 80% frequency of suspension of ALL maintenance therapy in the 29 patients who were HCV antibody positive, but only a 2% frequency of suspensions in those who were HCV antibody negative [7]. Thus, for these patients ALL therapy dose intensity was decreased when hepatitis C infection was present. An early randomized study by Pinkel et al. found that children with ALL who received full-dose of maintenance therapy had a longer median duration of complete response and greater likelihood of complete remission at the end of therapy than a group who were treated with half-dose maintenance therapy [39]. Recently both Italian and German investigators reported a greater event-free survival among ALL patients who received a higher portion of the intended maintenance therapy [40,41]. Potentially, early recognition and treatment with Ifn-α of acute HCV could allow delivery of a greater dose intensity of antileukemia therapy.

The experience with this patient demonstrates that Ifn-α can be given simultaneously with leukemic therapy. Our single patient had an efficacy and tolerance to Ifn-α that is within the range of findings reported for subjects who were not receiving antineoplastic therapy. The simultaneous administration of Ifn-α and antineoplastic therapy may allow the delivery of a greater proportion of planned therapy, with greater dose intensity and a decreased frequency of disease recurrence.

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